REMARKS

After entry of the instant amendment, claims 20 to 28, 30 to 33 and 35 to 39 will be pending. Claim 34 has been canceled, without prejudice. Claims 20, 30 and 33 have been amended. Claims 35 to 39 have been added. Support for added claim 35 may be found, for example, at page 5, lines 24 to 27. Added claims 36 and 37 are supported, for example, by the disclosure at page 11, lines 14 to 17. Added claim 38 finds support, for example, at page 5, lines 17 to 22 and page 8, line 12. Added claim 39 is supported, for example, at page 20, line 21 to page 24, line 12. No new matter is added.

In the Office Action dated October 10, 2006, the pending claims were rejected over Rickey et al., U.S. Patent No. 5,792,477 ("the 477 Patent") in view of Shimizu et al., U.S. Patent No. 5,824,339 ("the 339 Patent") or Yajima et al., U.S. Patent No. 5,972,373 ("the 373 Patent"). To the extent these rejections would be applied to the claims as amended herein, Applicants respectfully traverse.

Description Of The Problem Underlying The Present Invention

When administering a controlled release preparation to patients in the fed state, food related dose-dumping may be encountered. The problem of food related dose-dumping in fed patients can be attributed to a lot of factors. One of these factors is surely the mechanical forces that are exerted by the stomach on its content and thus on an ingested preparation. Another factor appears to be the *ionic strength* of the gastro-intestinal juices. Since the ionic strength values encountered in the gastro-intestinal tract vary not only with the region of the tract, but also with the intake of food, a controlled release formulation should preferably provide a controlled release profile, and in particular avoid dose-dumping, regardless of whether the patient is in fasted or fed conditions.

Applicants have found that the use of pregelatinized starch in a hydrophilic matrix formulation can counter the impairing or even destroying effect that the ionic strength of a release medium may produce. Said impairing effect of ionic strength on the controlled release profile of a hydrophilic matrix formulation may be attributed, as indicated in the specification (*see, e.g.*, page 3, line 33 to page 34, line14), to changes in the hydration of the viscous hydrophilic matrix polymers. Said matrix polymers have to compete for hydration

water with the solutes making up the ionic strength of the release medium. Consequently, the polymers may not hydrate to such extent as to ensure formation of matrix with acceptable resistance to disintegration. Hydration of the matrix polymers may largely or even completely be suppressed so that the matrix disintegrates almost immediately, e.g. within a time interval of 15 min after administration in the release medium. By incorporating pregelatinized starch in the formulation, the controlled release of active ingredient(s) from a hydrophilic controlled release formulation can be safeguarded or maintained in release media of changing ionic strength.

Response to Rejections

The 477 Patent is directed to microparticles that comprise 9-hydroxy-risperidone and a polymeric binder such as poly(glycolic acid) or poly(lactic acid), or the like (477 Patent at col. 5, lines 32 to 40). The 477 Patent further teaches that a surfactant or hydrophilic colloid, such as carboxymethylcellulose or poly(vinyl pyrrolidone) may be added to the processing medium used to prepare the microparticles, but it is not clear how much, if any, of these materials remain in the finished microparticles.

The 477 Patent does not describe solid oral dosage forms that comprise either the pregelatinized starch or viscous hydrophilic polymers. Indeed, the 477 Patent appears to be directed to repository formulations suitable for administration by injection (477 Patent, at col. 17, lines 41 to 48), not to oral formulations, such as tablets. Thus, the reference fails to address problems associated with maintaining a controlled release of an active ingredient when confronted with media of changing ionic strength, such as may be encountered along the gastro-intestinal tract in fasted or fed conditions.

Combination of the 477 Patent with the 339 Patent does little to overcome these deficiencies. The 399 Patent purports to disclose an effervescent composition comprising a core/shell powder made up of a fine granular core spray coated with a liquid mixture containing a water soluble polymer combined with a drug (339 patent at col. 6, lines 25 to 30). The fine granular cores may be made from a variety of materials, including a mixture of lactose and pregelatinized starch (339 Patent at col. 4, lines 16 to 18). The polymers used in the coating may include hydroxypropyl cellulose and hydroxypropylmethylcelluolose (339

Patent at col. 4, line 55 to col. 5, line 9), and optional additional ingredients, including binders such as pregelatinized starch (col. 6, lines 40 to 41).

The 339 Patent contains no teaching or suggestion, however, of the use of pregelatinized starch in an amount sufficient to enable the formulation to maintain a controlled release of the active ingredient in media of changing ionic strength, such as may be encountered along the gastro-intestinal tract in fasted or fed conditions. Indeed, the 339 Patent makes absolutely no mention of the impact that media of differing ionic strength may have on release of the active ingredient, nor does it suggest any solution to this problem.

Moreover, the Office Action fails to show explain how the 339 Patent may be combined with the 477 Patent. The 477 Patent is directed to microparticles prepared by a microemulsion/solvent extraction process. The 339 Patent, on the other hand, is directed to granular cores that are spray coated with a polymer/drug coating. The Office Action states that "One of ordinary skill in the art would have been motivated to include the viscous hydroxypropyl cellulose polymers of the '339 reference in order to improve the stability of the microparticle formulation" but ignores the fact that these polymers have an entirely different purpose in the 339 Patent than is disclosed for the surfactants and hydrophilic colloids in the 477 Patent. Moreover, even if that substitution were made, it is not clear how the requirement for pregelatinized starch would be met, or how the use of pregelatinized starch would fit into the microemulsion/solvent extraction process described in the 477 Patent. The Office Action simply fails to adequately resolve how these two completely disparate teachings could be combined to produce a formulation such as that recited in the pending claims, or why those skilled in the art would be motivated to combine the references as suggested in the Action.

In addition, Applicants note that whatever product might be produced by such a combination, it would clearly NOT be a tablet containing a controlled release matrix comprising a substantially homogeneous admixture comprising the active ingredient, the one or more viscous hydrophilic polymers, and the pregelatinized starch, as recited in added claim 39. At best, the combination of the 477 Patent and the 339 Patent, even if properly motivated, would result in microparticles or fine granules having the ingredients separated in a core and a coating, not the tablet recited in the added claim.

The teaching of the 373 Patent also fails to establish the prima facie obviousness of the claimed subject matter. The combination of the 477 Patent and the 373 Patent was cited only against claim 31. Although this reference suggests that pregelatinized starch may be included as a binder, there is no teaching or suggestion of the use of pregelatinized starch in an amount sufficient to enable the formulation to maintain a controlled release of the active ingredient in media of changing ionic strength, such as may be encountered along the gastro-intestinal tract in fasted or fed conditions. Indeed, like the 339 Patent, the 373 Patent makes absolutely no mention of the impact that media of differing ionic strength may have on release of the active ingredient, nor does is suggest any solution to this problem. Accordingly, the combined teachings of the 477 and 373 Patents, even if motivated, fail to establish the *prima facie* obviousness of the claimed subject matter.

CONCLUSION

The foregoing represents a *bona-fide* attempt to address all issues raised in the Office Action dated October 10, 2006. Applicants respectfully submit that the application is in condition for allowance. Accordingly, a Notice of Allowability for all of pending claims 20 to 28, 30 to 33 and 35 to 39 is earnestly solicited.

If the Examiner believes an interview would expedite prosecution of this application, the undersigned may be contacted at 215.564.8392 to arrange an interview.

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